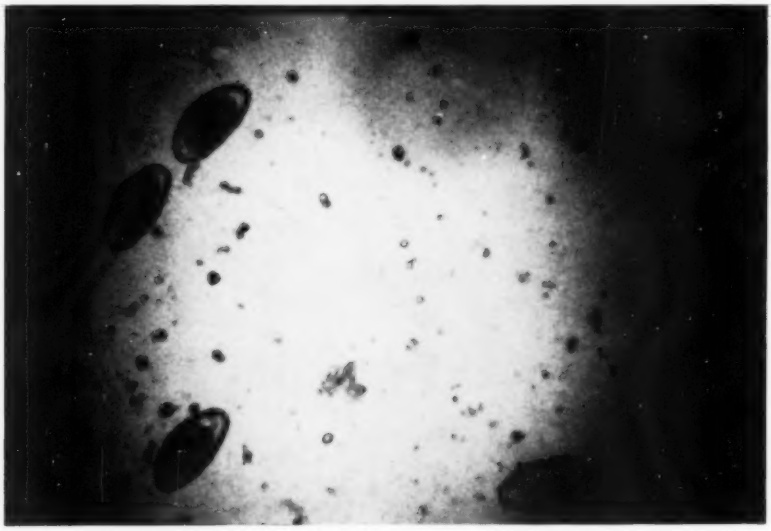
# American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



The Ova of Enterobius vermicularis

(See Editorial)

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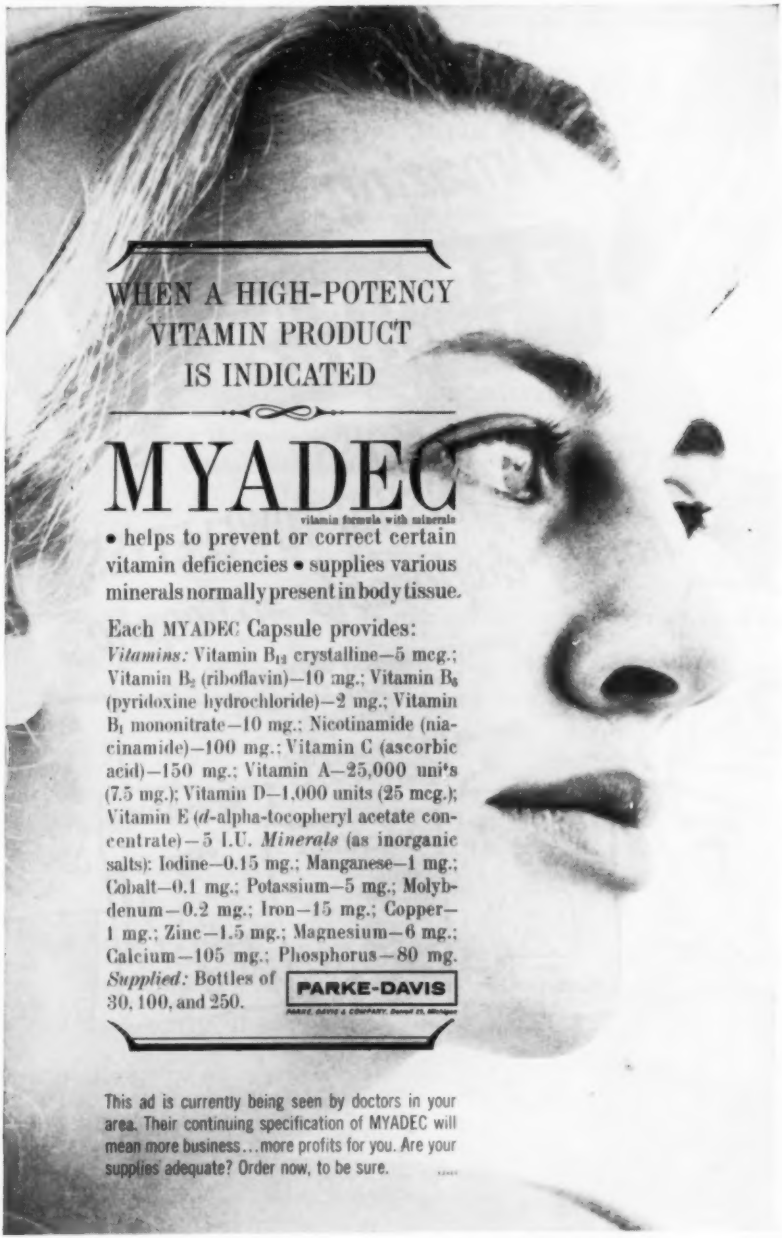

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# AMERICAN JOURNAL OF PHARMACY

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Since 1825



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Vol. 133 NOVEMBER 1961 No. 11


CONTENTS


Editorial

Piperazine OTC? ..... 376

Articles

Full Speed To Frustration. By H. C. McAllister ..... 378

Histological Studies of the Genus Lavandula. Part V. Section Spica. By J. K. Bhatnagar and M. S. Dunn .. 387

Chemotherapeutic Control of Acute Leukemia: III. Miscellaneous Agents. By J. R. Sampey ..... 395

Book Notices ..... 401

# EDITORIAL

## PIPERAZINE OTC?

THE proposal that piperazine for use as an anthelmintic be released for over-the-counter sale can hardly be taken seriously. While the Food and Drug Administration must give proper recognition to the petition of the company wishing to so market this product, it would seem almost certain that permission to do so will be denied.

Piperazine as the citrate, or some other suitable salt, is undoubtedly one of the least toxic anthelmintics and it is fairly effective against pinworms and to a lesser extent against the usual species of roundworms. It is not of value in tapeworm or hookworm infestations. The proper diagnosis and treatment of intestinal helminthiasis is anything but simple. The fact is that many physicians hesitate to attempt it since the examination of feces for ova and their proper identification is neither easy nor pleasant. Differentiation of the ova of various parasites requires considerable experience and skill and, even after diagnosis, treatment often must be repeated several times to be fully effective.

In the case of pinworm infestation, whole families are often involved and unless treated simultaneously it is almost impossible to eradicate the parasites. Roundworms are frequently traceable to pets in the home, usually dogs, and the same species affecting them infests man.

On the lay side of the picture, children who are irritable or who sleep poorly are often said to "have worms" and dosed accordingly, following the advice of grandmother or some equally empiric counselor. The same diagnosis is often made concerning the child suffering with malnutrition usually because of a poorly chosen diet.

All in all, the problem of worm infestation is a difficult one surrounded as it is by complexities in diagnosis and treatment by the medical profession and over simplification by the laiety. The answer does not lie in making one useful anthelmintic more readily available. The truth is that all anthelmintics should be restricted to prescription use. By its very nature, an anthelmintic must possess some toxicity.

If it did not, the worms themselves would be unaffected. Few anthelmintics, if any, are safe if used too often or in excessive doses, and there undoubtedly is some tissue damage or irritation in the intestinal lumen. Absorption of such drugs even though poor must result in some action on the liver, kidneys, or other tissues. Some of the oldest anthelmintics such as santonin are so toxic that they are rarely used by the physician for this very reason.

As it looks to us, there is just as much logic in releasing penicillin or erythromycin tablets for over-the-counter sale for the self-diagnosis and treatment of gonorrhea as there is in the release of piperazine for helminthiasis. The time is rapidly approaching when the Food and Drug Administration, together with the health professions, must take a hard look at the entire situation regarding the over-the-counter sale of drugs. These products have become big business with their advertising and promotion not always predicated upon scientific fact and public welfare.

Drugs which are simply palliatives and are well known by the public to be so may indeed be justified for sale to the public with certain limitations. On the other hand, drugs which are specifics presupposing accurate diagnosis should never be. Piperazine surely falls in the latter category.

With the expanding interest in over-the-counter products and with some which until recently were prescription products, it seems essential that a new category of drug products be established. This has already been proposed by others. This new category would be over-the-counter products restricted to sale by pharmacists. Such a restriction would give some professional supervision and would at least provide the opportunity for professional guidance as to use if it were needed or requested.

Even if this new category were established, anthelmintics including piperazine should remain on "prescription only" status. The pharmacist can no better diagnose helminthiasis by questioning the customer than can the layman. The truth is neither can the physician; he, however, has diagnostic facilities available which makes correct scientific treatment possible. This should be the aim of all drug therapy.

L. F. Tice

# FULL SPEED TO FRUSTRATION *

By H. C. McAllister **

I AM indebted to your program chairman for his kind invitation to attend this meeting. It is with much gratitude also to the N. A. B. P. that I can express to you my pleasure at being here—and it is a real pleasure.

From the title I have selected, I rather suspect that some of you have already concluded that I am just another one of pharmacy's many heretics, who comes seeking to impose his troubled thoughts upon your well-defined and smooth-operating professional objectives and functions. I only wish that this were so—in which case I would gladly accept the charge of heresy. But I believe that pharmacy's situation is such today that we can ill afford the luxury of this complacency.

For a number of years, we have heard the statement, "Pharmacy is at a crossroads." This was indeed true. It now appears that we have passed that crossroads, but perhaps not too far that we can and should stop and read the signs to determine whether we have taken the right road.

The fact that various segments of pharmacy have taken different roads is self-evident. For our purposes here, I have reference to the community pharmacist. Is he on the road that will take him where he wants to go? The signs which mark our present course can be compared to our highway signs—there are many kinds, and occasionally they are obscure and confusing. But let us stop to read some of these signs.

## The Public Image of Pharmacy

We have heard so much on this subject in recent months that it has almost become boring. The mere sound of the words seems

* Presented at District No. 2, Boards & Colleges of Pharmacy, Williamsburg, Va., Nov. 3, 1961.

** President, National Association of Boards of Pharmacy, and Secretary, North Carolina State Board of Pharmacy (P. O. Box 471, Chapel Hill, N. C.).

to cause a feeling of resentment. But isn't this about the reaction a not-too-handsome individual gets if he sees his own picture too often or too long? Might we ask "What has happened to this individual called pharmacy, who only a few short years ago was known and loved by everyone? Has he really grown into this monster that the antitrust law is after and that the watchdogs of FDA must constantly guard that he doesn't assault the public—a monster the public resents when it must employ his services?" Shall I go on about the public image of pharmacy? I think not, but I do feel we cannot afford to ignore some very important facts relating to pharmacy's present situation and to its future.

In a recent issue of the N. A. B. P. Bulletin, I pointed out to you that we had traditionally accepted the proposition that pharmacy had to subsidize itself, its professional functions, through the sale of commodities; and how, through the extension of this activity in our quest for economic security, we have tended to destroy that which we sought to secure. At the expense of being repetitious, I ask your indulgence that we might examine this matter in more detail.

For years, the proposition of commercialism vs. professionalism has been debated in the forum of pharmacy's professional and trade organizations. It has also been dealt with in our press. We became excited or wrought up, in order, over the chain store, cut-rate stores, merchandising techniques, self-service, solely professional pharmacies and now discount and mail order houses. Some say that we have weathered all of these storms and have come out stronger for the experience. Others are not so sure. They think that perhaps this house which we now occupy is gaudy and flimsy, and that it will doubtless be largely destroyed in the first wave of an economic storm of depression. My purpose here is not to debate the question of commercialism vs. professionalism, although it needs desperately to be resolved. For now, however, let us examine some of the effects which seem to have resulted from over-commercialization.

Few of us here today are so young that we do not remember when we conducted a drug store or pharmacy in which we had departments—baby department, first aid department, sick room supplies, camera department, etc. It was one organization, with a few departments centered around and supporting our principal purpose—pharmaceutical service. What is the trend today? Bigger, shinier, wider variety stores with a prescription department. Our foremost reason

for existence has been minimized and relegated to the status of a department and, in many instances, a very minor department in a good-sized business enterprise. The words "drug store" or "pharmacy" have even been deleted from the names of the outlets of at least two giant chains. With these things occuring, is it any wonder that supermarkets, variety and department stores, and even discount houses are seeking to establish prescription departments? The kind and character of these places where pharmacy is practiced is having its deadly effect on you and your profession. Frustrating? Yes.

Let us consider for a moment what these changes have done and are doing to the individual pharmacist. A short ten years ago every pharmacist who was licensed, and who had the inclination and a reasonable amount of energy, could hope to own his own pharmacy. To a lesser extent, this is still true today in some areas. But let us take a look into the immediate future to see what opportunities are likely to be available if present trends continue.

Changes in our socio-economic life have brought about many changes in living patterns. One of the most significant changes which has occurred insofar as we are concerned is the development of the shopping center. (What will be said about shopping centers applies equally to business renewal districts.) One of the basic units in the planning of any shopping center, large or small, is a drug store—not pharmacy. The manner of financing these shopping center developments is such that long-term, high-rent leases must be obtained. These in turn are used as collateral for development funds. Only those pharmacists who have demonstrated their ability for financial success can qualify for these leases. The individual pharmacist who has done this is usually to that point in his career that he does not care to undertake new ventures. As a result, the lease goes to big and well financed organizations who operate a store with a prescription department. This is not all of the picture. To meet the rent payments and to realize a profit on investment, the matter of business volume becomes one of primary consideration. So what do they do? They stock anything that will sell. They use "come-on" gimmicks, loss leaders, or any other of the hundred and one tricks to create traffic on which they hope to unload some of the junk with which they have now cluttered up the place—garbage pails, antifreeze, shrubbery, or war surplus. What does all of this do to the public image of pharmacy?

And, again, this is not all. There is more that is happening and will happen to you as individual pharmacists. This past year, our schools of pharmacy throughout the nation admitted the first classes that will spend five years studying for a degree in pharmacy. When these boys and girls have finished their course, they will be well educated and qualified to perform a high level of professional service. They will then locate in practice. Will they be able to fully utilize their knowledge and training or will they be required to sell garbage pails and war surplus? Unless conditions are provided wherein these men and women who have launched themselves in a professional career can utilize their talents and abilities, they will most certainly become frustrated and disillusioned. This is when the labor unions step in. The unions will say to these young people "Look, we can provide conditions under which you will have to do nothing but fill prescriptions, and leave the junk to others." What I have just said is not idle speculation. It has actually already happened in some areas of this country. Is this the public image you want for the pharmacists—a unionized guild of tradesmen?

## Federal Antitrust Suits

As one of the persons who was subpoenaed to testify in the suit brought by the government against Donald K. Hedgpeth and the Northern California Pharmaceutical Association, I found it necessary to inform myself on just what these suits were all about. I learned that the federal antitrust laws were enacted to deal with monopolies, which result in the restraint of trade. The indictments served on the defendants say that the Association and certain individuals in that state were conspiring, through recommended price schedules for prescriptions, to restrain *trade*. What these indictments really say is that the defendants are fixing prices on commodities. No mention is made of any *professional service* rendered in connection with the *prescription commodity*. The antitrust laws have not been interpreted to apply to professional service. Indeed, the court said, "There is an immunization under the statute (Sherman Act) for professional services (and) if what these pharmacists do is entirely a matter of professional service, why I think the court should keep hands off of it." But then the judge also added, "But I don't think any experts would convince me that this is a professional service. A prescription is only a piece of paper—that requires no more professional service from the

druggist than putting it in the package and delivering it." The court had more to say about the lack of professional stature of the pharmacist when it referred to his membership in labor unions. Could it be that the court views pharmacy as a unionized guild of tradesmen? I should like to say at this point that I went to San Francisco with an eight-page typewritten outline of the things the pharmacist does when he fills a prescription. From these notes I was in a position to testify for several hours on this subject, but I was permitted to answer only four questions, three of which had to do with my identity. After the fourth question, which was related to the purpose of my being there, the judge threatened the defense counsel with contempt of court and said, "I consider this to be an undue waste of time of the jury and court in this case . . ." As I interpret these statements, the court has said, in effect, "Prove that you are a profession if you can, but the court doesn't have time to listen to your proof." Is this not a frustrating position in which we find ourselves? The case has, of course, gone up on appeal. But if the government wins this case, it will in effect establish that pharmacy is not a profession; and it will be extremely difficult, if at all possible, to *prove legally* that the situation is other than this. Your professional function is then reduced to the distribution of a trade commodity. Where does this leave you and your future professional aspirations? I need not answer this for you, because you know that it leads straight down the road to frustration.

Within the past few days, and since this paper was prepared, an additional sign has been posted in the form of a stipulation in the Utah case. Here the government has agreed that pharmacy is a profession. We shall anxiously watch this sign for further direction.

There are yet more signs that must be read and interpreted.

### Federal Food, Drug, and Cosmetic Act

The passage of the Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act (which incidentally was opposed by certain farsighted elements in pharmacy) considerably modified the basic philosophy which was understood to support the act itself and which was endorsed and worked for by organized pharmacy. The Durham-Humphrey Amendment originated with a pronouncement of one of the FDA officials that a prescription was like a check. Once it had been cashed, it could not be cashed again. Of course, this state-

ment is right for checks; but it is not right for all prescriptions for all drugs. This amendment has operated to effect changes in our profession which result in denying the pharmacist the right to exercise professional judgment in his day-to-day practice. Full compliance with the law places him in a position of intolerable frustration, especially with regard to refilling prescriptions. In order to carry out his work adequately, he has had to reach "understandings" or "make arrangements" with physicians relative to refilling certain types of prescriptions. All of you know what is referred to here. You and your patrons are constantly inconvenienced and you are often abused because of your desire to comply fully with the law. Evidence of the pharmacist's dissatisfaction with the present unrealistic requirements of the law and its administration is reflected in the resolutions calling for change which have been passed by state, regional, and national pharmaceutical organizations. Patient and pharmacist inconvenience is only part of the story. What is perhaps more important from our point of view is the effect that these things are having on professional practice. It is beneath the dignity of the profession for its members to have to resort to "arrangements" with physicians in order to fully discharge their functions, and there is serious question as to whether these "arrangements" would meet the test of compliance with the law and the regulations promulgated thereunder. There is something badly out of adjustment when our profession must be constantly faced with the liability of violation of law in order to adequately perform the functions that are expected of it by the allied professions and by the public. The ultimate position of the pharmacist under the present arrangement becomes simply that of a technician, and we are moving rapidly toward that position under the present and ever-increasing restrictions. All of you are familiar with the most recent pronouncement and enforcement activities relative to physicians' samples.

No one wants adequate and *proper* controls on the distribution of drugs more than does the pharmacist. Proof of this fact is self-evident in the many laws that he has sponsored in this area. The value of restrictive requirements breaks down, however, when these requirements become unrealistic and in some instances unreasonable. The suggestion has been made that relief for the pharmacist from this burden can be had by several relatively simple changes in the Food, Drug, and Cosmetic Act. Permit me to digress for a moment to enumerate these. They would simply reclassify drugs as follows:

Class A—Present legend drugs with present restrictions.

Class B—Drugs dispensed on prescription, which prescription might be refilled through the exercise of professional judgment for a specified, limited number of times and under a stated time schedule.

Class C—Drugs which might be sold without prescription but only by or under the supervision of a pharmacist. This class would include those drugs which have been removed from the legend requirement and other drugs such as the potent antihistamines, which may now be sold indiscriminately in most states, etc.

Class D—Drugs which can be sold without other than labeling restrictions, as at present.

Making the changes in the law such as have been suggested would not only *not* weaken the usefulness of the law, but would tend to create more respect for the law and to secure better compliance with it as a result of the removal of unreasonable features. Most important of all, would not the public be better served by the elimination of unwarranted delays which presently create irritations, frustrations and, in some instances, even anxieties? One thing is sure—the present status of the law is adding momentum to the practicing pharmacist's unwilling drive down this route to frustration.

Here is another road sign which appears to warn of a detour. It reads:

**Mail Order Prescription Services**

It is unfortunate that the fallout from the inaccurate publicity associated with what has come to be known as the Kefauver Hearings continues to rain down upon us. In spite of the fact that the Department of Labor statistics show the per cent of expendable income of the average family today being spent on drugs to be five per cent less than it was in 1939, a significant segment of our population has been convinced by this sensational publicity that it is being overcharged, even gouged, for prescription drugs. This situation has produced an atmosphere in which there seems to be developing all sorts of unorthodox drug distribution plans. One of these is the mail order prescription service. This mail order arrangement is another

instance in which the professional service of the pharmacist is minimized and in the mind of the patient it may be eliminated entirely. He receives a commodity from an impersonal business house. He pays, he believes, only for a commodity. But what is more important than the devaluation of professional service is the total destruction of the all important physician-patient-pharmacist relationship which is such a necessary consideration in medication control. What has been said about the mail order mechanism applies also to the drug distribution plans of the several voluntary specific disease associations. I know that it is unnecessary for me to convince you of the dangers associated with the mail order and other unorthodox prescription services. What I don't know is whether all of you fully realize the seriousness of the threat. This seriousness was underscored in July of this year when Spiegel, Inc. announced its "non-profit" prescription plan. (I wish I had time to tell you something of what we have learned, not only of the "non-profit" aspect of this plan, but also of the serious dangers associated with it. Perhaps this will become known in due time.) Now that Spiegel has entered the field, will Sears, Montgomery-Ward, or some of the others follow? Are the vast knowledge and truly wonderful therapeutic achievements as represented in today's prescription drugs to become items in a mail order catalogue or merchandise in a vending machine? Frustrating? Frankly, yes.

There are still other signs, which read: Generic Equivalents, Health Department Dispensaries, Industrial Health Services, Union Health Services, Nursing and Rest Homes, and on and on. I think, however, we have read enough of these signs to know where we are headed. Whether or not we continue on this course is up to us.

In Dicken's *Christmas Carol,* Ebenezer Scrooge had three very real dreams. When he awoke, he wanted to go back and rectify some of the mistakes he had made, and did so. The picture which has been drawn for you is no dream—it is grim reality. Fortunately, however, we have not yet traveled this road so far that it is not possible to take a different course.

I would not presume to be so wise as to undertake to point out the direction and route that pharmacy should travel. This I do know, however; pharmacy must know where it wants to go.

Presently, there appears to be no general understanding and agreement among the several members of this family of ours as to

its desired destination. Some have talked about that general area of dignity and satisfaction called profession. Some seem determined to seek the green pasture of commercialism, which is so full of action and excitement, and where there are many other people who are anxious to join the free-for-all contest that is going on there. Still others seem to be going along just for the ride, not knowing what else to do and thinking that somehow, eventually, this journey will end safely and well. It seems to me that the time has arrived when someone in this group must undertake the job of getting some organized thinking done with the view of setting a definite destination and deciding on the best course by which it can be reached. Unless this is done, and pretty soon, we may find that we will have to abandon the vehicle entirely and each walk his separate way. The road is getting rough and fuel is low.

Each of us here today has a responsibility in this matter. The fact that you are here is evidence of your interest. But haven't all of us concerned ourselves too much with our own immediate sphere of interest and responsibility, perhaps to the neglect of the mainstream of our course? It now becomes imperative that we chart this course—that we define a national purpose and that we then do those things that are necessary to implement this purpose. (At the Eighth Annual Joint Pharmacy Seminar held this year at Wayne State University, my predecessor in this office made some splendid suggestions as to how we might go about this project.) I wish I could go further and say that the practicing community pharmacist is the key individual around whom our interests should be centered, but I am not sure. I know that he needs much attention, but is he the key to our future? I don't know. Public patterns and attitudes have so changed that it might make such a designation unwise. I sincerely hope not. In making a decision, it will be extremely difficult to avoid emotional influences, but the decision we must make and soon. If we fail to do this, we can do no other than continue full speed to frustration.

# HISTOLOGICAL STUDIES OF THE GENUS LAVANDULA

## Part V. Section SPICA

## Some Comparative Quantitative Values for the Leaves of Lavandula officinalis Chaix, L. latifolia Vill., and L. lanata Boiss.

By J. K. Bhatnagar * and Marin S. Dunn **

### Introduction

IT has been stated in an earlier report (1) that the leaves of *L. lanata Boiss.* may be distinguished from the leaves of *L. officinalis Chaix* and *L. latifolia Vill.* by the presence of characteristic large nonglandular hairs and the striated cuticle on both the epidermal surfaces.

The leaves of *L. officinalis* and *L. latifolia* did not show histological features of pronounced diagnostic value. The identification of these two species is at present based primarily on the differences found in the bracts, the bracteoles, and the size of the calyx and corolla tubes of their flowers.

The data presented in this report were obtained during the course of the exploratory investigation undertaken to find some characteristics, other than those already known, which could be used to differentiate these two species. As *L. lanata* can be histologically differentiated from the other two species, the data concerning *L. lanata* are not given in full detail in this report although they have been summarized in Table V.

The four different sets of values studied and reported herein are the epidermal count, the stomatal ratio, the palisade count, and the palisade ratio. Of these, the palisade ratio was determined by the usual method (2). The other values studied have been defined and the methods for their determinations, described under "Material and Methods" of this report.

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## Material and Methods

The sources of the materials used in this study are the same as have been listed in the Table 1 of an earlier report (1).

The fresh material was cleared by the method of Arnott (3). The cleared material was mounted in a mixture of equal volumes of glycerine and strong solution of chloral hydrate (70 Gm. in 30 ml. of water) for temporary mounts. For some permanent mounts, the material was first washed free of chloral hydrate with water, and then mounted in glycerine jelly mounting medium.

*Definitions:*

The epidermal count is the average number of epidermal cells, including the glandular and the nonglandular hairs but excluding the stomata, that are present in a given unit area.

The stomatal ratio is the percentage of the epidermal cells which are modified into stomata, the two guard cells and the ostiole being taken as a single unit, and is calculated by using the formula, $\frac{S}{S+E} \times 100$, where E equals the number of epidermal cells in a given unit area, and S the number of stomata in the same area. Thus, in essence, the stomatal ratio is similar to the stomatal index (4) except for the difference in the method of counting the cells. For

TABLE I

A Typical Data-Sheet Used to Determine the Epidermal Count and the Stomatal Ratio

Name of the species, *L. officinalis Chaix*

Serial No. of the specimen 1 Source of the specimen L *

| No. of fields examined | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total | Range |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Epidermal cells ** | 28 | 23 | 21 | 20 | 20 | 20 | 19 | 19 | 19 | 18 | 207 | 18-28 |
| Stomata | 3 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 16 | 1-3 |
| Glandular hairs | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 0-1 |
| Nonglandular hairs | 8 | 7 | 9 | 5 | 6 | 9 | 8 | 7 | 5 | 6 | 70 | 5-9 |

* The sources of the material used are the same as have been listed in an earlier report (1).

** The epidermal cell total includes the glandular and the nonglandular hairs.

calculating the stomatal index, a total of approximately four hundred epidermal cells are counted; whereas, for stomatal ratio, the total number of epidermal cells and the stomata in ten different fields of a given unit area, selected at random, are ascertained and used in the formula mentioned above.

The palisade count is the average number of palisade cells underneath 0.01 sq. mm. of the epidermal surface.

The palisade count differs from the palisade number reported for some *Labiatae* by earlier workers (5) who defined the palisade number as the average number of palisade cells, that are 50 per cent or more within the area of a single square of the Howard eyepiece micrometer disc.

TABLE II

THE EPIDERMAL COUNTS AND THE STOMATAL RATIOS FOR THE LEAVES OF *L. officinalis Chaix* AND *L. latifolia Vill.*

| Name of the species | *L. officinalis Chaix* | | | | | *L. latifolia Vill.* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Serial No. | 1 | 2 | 3 | 4 | 5 | 20 | 15 | 21 | 17 | 12 |
| Source of specimen | L | I | D | A | E | E | F | F | C | K |
| Total epidermal cells in 10 fields (E) | 207 | 222 | 233 | 256 | 284 | 136 | 180 | 185 | 202 | 219 |
| Epidermal count for the specimen | 20.7 | 22.2 | 23.3 | 25.6 | 28.4 | 13.6 | 18.0 | 18.5 | 20.2 | 21.9 |
| Range | 18–28 | 18–29 | 21–27 | 19–37 | 22–32 | 11–15 | 13–22 | 16–20 | 15–25 | 16–27 |
| Epidermal count for the species | 24.0, Range 20.7 to 28.4 | | | | | 18.4, Range 13.6 to 21.9 | | | | |
| Total stomata in 10 fields (S) | 16 | 12 | 9 | 11 | 10 | 15 | 10 | 17 | 28 | 15 |
| Stomatal ratio for the specimen $= \frac{S}{E+S} \times 100$ | 7.17 | 5.13 | 3.72 | 4.12 | 3.40 | 9.93 | 5.26 | 8.42 | 12.18 | 6.41 |
| Stomatal ratio for the species | 4.71, Range 3.40 to 7.17 | | | | | 8.44, Range 5.26 to 12.18 | | | | |

*Method of Counting:*

For determining the epidermal count and the stomatal ratio, a 5 mm. square micrometer disc is placed in a 10x eyepiece. The outline of the grid as viewed through a 4 mm. objective is drawn on a sheet of paper with the aid of a camera lucida (Fig. 1, the outer larger square). The outlines of all the epidermal cells and the stomata, half or more within the area of the larger square are traced (Fig. 2) and counted. A minimum of ten different fields selected at random, from each individual specimen, are counted to calculate the average epidermal count and the stomatal ratio for the specimen.

For the palisade count, a square with a side equal to 0.1 mm. as measured with the help of a stage micrometer, is drawn using a camera lucida, a 10x eyepiece, and a 4 mm. objective (Fig. 1, the inner, shaded smaller square). All palisade cells half or more within the area of the smaller square are counted, and the average of ten different fields selected at random is taken as the palisade count for the specimen.

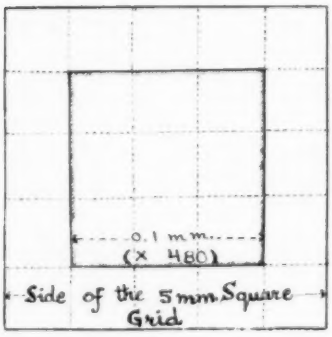


FIG. 1. The camera lucida outlines of the area of the grid used to determine the epidermal counts and the stomatal ratios (the larger square), and the palisade counts (the inner shaded square).

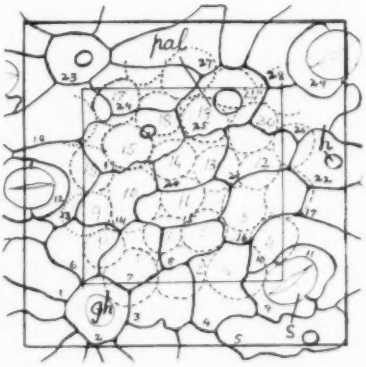


FIG. 2. Outlines of the cells of the epidermis showing the glandular hair, gh; nonglandular hair, h; and the stomata, s. The palisade cells, pal, are shown in dotted lines.

It was noted that, by using the above combination of lenses of the microscope, the combined length of the contiguous sides of the three squares of the 5 mm. square micrometer disc was equal to 0.1 mm. as measured on the stage micrometer. In other words, the area of the nine smallest squares (Fig. 1, small squares with dotted lines within the shaded area) was equal to 0.01 sq. mm. and could be used for finding the palisade counts.

TABLE III

THE PALISADE COUNTS FOR THE LEAVES OF *L. officinalis Chaix* AND *L. latifolia Vill.*

| Serial No. of specimen | Source of specimen | Number of the fields counted 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total in 10 fields | Palisade Count of the specimen | Range for specimen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *L. officinalis Chaix* | | | | | | | | | | | | | | |
| 3. | D | 10 | 12 | 14 | 15 | 17 | 17 | 17 | 18 | 19 | 20 | 159 | 15.9 | 10-20 |
| 2. | I | 16 | 17 | 17 | 18 | 18 | 18 | 19 | 20 | 20 | 21 | 184 | 18.4 | 16-21 |
| 1. | L | 17 | 18 | 18 | 18 | 18 | 19 | 19 | 20 | 20 | 21 | 188 | 18.8 | 17-21 |
| 4. | A | 17 | 18 | 18 | 18 | 20 | 22 | 22 | 23 | 24 | 25 | 207 | 20.7 | 17-25 |
| 4. | A | 19 | 19 | 20 | 21 | 21 | 22 | 23 | 23 | 25 | 27 | 220 | 22.0 | 19-27 |
| 10. | D | 19 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 27 | 27 | 241 | 24.1 | 19-27 |
| 5. | E | 22 | 22 | 23 | 23 | 25 | 25 | 25 | 25 | 26 | 29 | 245 | 24.5 | 22-29 |
| | | Palisade Count for the species | | | | | | | | | | | 20.6 | |
| | | Range | | | | | | | | | | | 15.9-24.5 | |
| *L. latifolia Vill.* | | | | | | | | | | | | | | |
| 20. | E | 7 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 10 | 89 | 8.9 | 7-10 |
| 17. | C | 11 | 11 | 11 | 11 | 12 | 12 | 13 | 13 | 13 | 13 | 120 | 12.0 | 11-13 |
| 18. | E | 13 | 15 | 16 | 16 | 17 | 17 | 18 | 18 | 18 | 19 | 167 | 16.7 | 13-19 |
| 15. | F | 16 | 16 | 16 | 17 | 17 | 18 | 18 | 18 | 19 | 20 | 175 | 17.5 | 16-20 |
| 21. | F | 14 | 15 | 17 | 18 | 18 | 19 | 20 | 20 | 21 | 22 | 184 | 18.4 | 14-22 |
| 12. | K | 15 | 17 | 18 | 18 | 18 | 18 | 19 | 21 | 21 | 22 | 187 | 18.7 | 15-22 |
| 14. | G | 17 | 17 | 18 | 19 | 19 | 20 | 20 | 21 | 21 | 21 | 193 | 19.3 | 17-21 |
| | | Palisade Count for the species | | | | | | | | | | | 15.9 | |
| | | Range | | | | | | | | | | | 8.9-19.3 | |

## Experimental

A typical data sheet used for finding the epidermal count and the stomatal ratio for each of the specimens examined is shown in Table I. The number of the epidermal cells recorded includes the numbers of the glandular and the nonglandular hairs.

In Table II, the epidermal counts and the stomatal ratios for the leaves of *L. officinalis* and *L. latifolia,* based on the average of five specimens for each of the two species, are given. Also included in the table are the ranges for these values for the individual specimens, and also the species.

The palisade count for the leaves of the above species, based on the average of seven specimens for each of the two species, is given in Table III, while the values of the palisade ratios, also based on the average of seven specimens for each species, are recorded in Table IV.

In Table V, the four values determined for the leaves of all the three species are recorded for the purpose of comparison. The data for *L. lanata* were obtained by exactly the same methods as used for the other two species.

TABLE IV

PALISADE RATIOS FOR THE LEAVES OF *L. officinalis Chaix* AND *L. latifolia Vill.*

| *L. officinalis Chaix* | | | | *L. latifolia Vill.* | | | |
|---|---|---|---|---|---|---|---|
| Serial No. | Source | No. of readings | Range of Palisade Ratio | Serial No. | Source | No. of readings | Range of Palisade Ratio |
| 1 | L | 46 | 1.25-3.75 | 11 | D | 46 | 2.00-4.25 |
| 2 | I | 34 | 2.50-5.00 | 12 | K | 39 | 1.50-3.25 |
| 2 | I | 44 | 1.25-4.30 | 15 | F | 44 | 1.75-3.75 |
| 7 | E | 53 | 1.00-3.00 | 17 | C | 37 | 1.25-2.25 |
| 4 | A | 53 | 1.25-2.75 | 18 | B | 16 | 1.25-2.25 |
| 5 | E | 35 | 2.25-4.25 | 20 | E | 28 | 1.25-2.75 |
| 10 | D | 55 | 1.75-4.00 | 21 | F | 20 | 2.00-3.75 |
| | | 320 | Range 1.00 to 5.00 (1.50-4.25)* | | | 230 | Range 1.25 to 4.25 (1.25-4.25)* |

* The values shown within brackets cover approximately 95 per cent of the readings and were obtained by eliminating infrequently occurring readings on either end of the range.

## Discussion and Summary

On the basis of the data summarized in Table V, the following remarks may be made with respect to the usefulness as diagnostic aids of the four values reported herein.

The epidermal count may be helpful in identifying *L. latifolia,* from *L. officinalis* and *L. lanata.* Though the values of the epidermal counts in the latter two species are closer to each other (24.0 and 26.7, respectively), yet these are noticeably higher, both in range and average value, than that of *L. latifolia* (18.4).

Likewise, the stomatal ratio of *L. officinalis* may be of value in distinguishing this species from *L. latifolia* and *L. lanata.* The stomatal ratio of 4.71 for *L. officinalis* is almost half that of *L. lanata* (9.47) and appreciably lower than that of *L. latifolia* (8.44).

The palisade count for *L. latifolia* and *L. lanata* are quite close (15.9 and 16.9, respectively) but are significantly lower than that of *L. officinalis* (20.6). The range of the palisade count in *L. officinalis* is also higher in both its minimum and maximum values than those of the other two species. Thus, palisade count may be of value in identifying *L. officinalis.*

TABLE V

SUMMARY OF THE VALUES OF THE EPIDERMAL COUNTS, STOMATAL RATIOS, PALISADE COUNTS, AND PALISADE RATIOS OF THE LEAVES OF *L. officinalis Chaix, L. latifolia Vill.,* AND *L. lanata Boiss.*

| *Values compared* | *L. officinalis Chaix* | *L. latifolia Vill.* | *L. lanata Boiss.** |
|---|---|---|---|
| Epidermal Count | 24.0<br>Range 20.7-28.4 | 18.4<br>Range 13.6-21.9 | 26.7<br>Range 23.6-29.9 |
| Stomatal Ratio | 4.71<br>Range 3.40-7.17 | 8.44<br>Range 5.26-12.18 | 9.47<br>Range 7.70-10.88 |
| Palisade Count | 20.6<br>Range 15.9-24.5 | 15.9<br>Range 8.9-19.3 | 16.9<br>Range 12.6-19.4 |
| Palisade Ratio | Range 1.00-5.00 | Range 1.25-4.25 | Range 1.25-1.50 |

* These values were determined in exactly the same manner as described for the other two species.

The palisade ratios for *L. officinalis* and *L. latifolia* are too close to be of any value as a diagnostic aid. In case of *L. lanata,* however, the maximum value of 1.5 of the range is very low as compared to the maximum values of 5 and 4.25 respectively, for *L. officinalis* and *L. latifolia,* and may be useful in identifying this species from the other two.

Thus, of the four values studied, the ones offering diagnostic possibilities are, the epidermal count for *L. latifolia;* the stomatal ratio and the palisade count for *L. officinalis;* and the palisade ratio for *L. lanata.*

**Acknowledgment**

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# CHEMOTHERAPEUTIC CONTROL OF ACUTE LEUKEMIA: III. MISCELLANEOUS AGENTS

By John R. Sampey *

FOLIC acid antagonists, adrenal steroids, and 6-mercaptopurine are the chemotherapeutic agents of choice in the management of acute leukemia, and a dozen other drugs have been employed on scores of patients (28, 29). While these established drugs are bringing relief to thousands of patients, the search for better agents continues apace, for as Karnofsky (17) has well expressed the situation: "Exploration of analogues of available types of compounds has not been rewarding, and very likely the major advances will be in discovering new classes of drugs." The present study records the results of a third search of the world's medical literature for new drugs to control this disease which strikes young and old with such suddenness and finality.

*2,4-Diamino-5-(3',4'-dichlorophenyl)-6-methyl pyrimidine.* This analogue of Daraprim has been employed by Burchenal (2) on 15 children with acute leukemia who had received no previous chemotherapy, and he reported some hematologic remission in three; however, no response was seen in 10 children who were resistant to amethopterin, and none of seven adults with acute leukemia was benefited; the drug was judged to be more toxic than amethopterin.

*Diaminopurine.* Burchenal (2) recorded some remissions in three of 26 patients with acute leukemia who were administered diaminopurine. Hibino and associates (14) observed no improvement in one patient given this drug.

*2-Amino-6-[(1-methyl-4-nitro-5-imidazolyl)thio]purine.* Rundles *et al.* (27) employed B.W.57-323 with prednisone in 13 patients with acute leukemia to induce five complete remissions, one good, one fair, and two questionable responses; the complete remissions lasted from two to 10 months. Elion *et al.* (6) reported a leukopenic response in adults with acute leukemia who received the drug. Ellison and Tan

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(7) treated 12 adults and 15 children with B.W.57-323 and recorded partial remissions in four adults and two children, but four of these continued for only one month or less; none of 10 children who were resistant to 6-mercaptopurine responded.

*6-Azathymine.* Ellison *et al.* (8) observed that 16 patients with acute leukemia failed to respond to this thymine analogue.

*Azaguanine.* Osamura and Ito (23) noted clinical remissions for 0.4 month in two patients with acute granulocytic leukemia, following azaguanine treatment. Hibino *et al.* (14) found the drug ineffective in one patient.

*Thioguanosine.* Krakoff *et al.* (18) tabulated one complete remission, two partial hematologic remissions, and three clinical responses in 14 adults who were given thioguanosine; they reported that none of 12 children had complete hematologic remissions to this therapy.

*Azauracil.* In a report from the Cooperative Clinical Research Program of the Cancer Chemotherapy National Service Center (4), 6-azauracil was found to be ineffective in 42 patients with acute leukemia. Freireich *et al.* (11) concluded that there was no significant antileukemic activity of this drug in 28 cases of "advanced refractory" acute leukemia, and Waelsch (31) observed negative results in two other cases of acute leukemia administered 6-azauracil.

*6-Azauridine.* Finch *et al.* (10) described reduction in circulating leukocytes in all six patients administered 6-azauridine but leukemic marrow infiltration persisted in all with the possible exception of one; some fair clinical responses were noted; three showed marked reduction in lymphadempathy, clearing of the skin in two, etc., but there were no complete remissions. Welch *et al.* (33) reported a fall in white blood cells in 11 of 12 patients given this drug; also, they noted decreased percentage of blasts in six of 12, marrow improvement in one of 12, increased platelets in one of eight, regression in cutaneous lesions in two out of two patients, and decreased splenomegaly in two of four.

*5-Fluoro-2'-deoxyuridine.* Murphy *et al.* (20) gave 24 children and four adults a preliminary trial of 5-FUDR: four children whose acute leukemia was resistant to 6-mercaptopurine and methotrexate

had complete bone marrow remissions, and one had a partial response; one adult experienced a brief hematologic improvement but a severe toxic reaction set in. Wolman and Gens (34) described a partial remission in one of five children with lymphoblastic leukemia, after 5-FUDR therapy. Papac *et al.* (25) reported that 5-FUDR but not the 5-iodo-derivative induced partial remissions in adults with acute leukemia and, in a second report (24), they described a potentiating effect on the blood response in patients receiving both drugs.

*Ethyleneiminoquinones.* Obrecht (22) described some subjective improvement in a patient with acute leukemia, following treatment with Bayer A 139, but objectively the patient grew worse. Gerlich (12) noted no sign of increased cellular maturation in eight patients given triethyleneiminobenzoquinone, and Linke (19) reported four good and eight fair remissions in 23 patients with acute myelocytic leukemia after administration of this drug.

*ThioTEPA.* Takahashi *et al.* (30) observed that acute leukemia responded clinically to treatment with triethylene thiophosphoramide. Hibino *et al.* (14) induced a partial remission in one patient with Thespamin, but Hammer (13) found the drug ineffective in one patient.

*Triethylammonium Bromide.* Benko (1) reduced the white blood cells in a patient with subacute leukemia by administering TEAB.

*Triamcinolone.* This chemical induced two partial hematologic remissions and one clinical remission in three patients with acute lymphocytic leukemia in a report by Carvalko *et al.* (3); they found also that two of four patients with hemocytoblastic myeloid leukemia responded, but four myeloblastic and one paramyeloblastic forms failed to improve.

*Psicofuranine.* Costa and Holland (5) observed no effect on tumor growth in one patient with acute myelocytic leukemia after administration of psicofuranine.

*Narcotine.* The Cooperative Clinical Research Program of the C. C. N. S. C. reported that narcotine was ineffective in seven patients of all ages who had acute leukemia.

*Testosterone.* Musmeci and Nofri (21) noted that this male hormone had little effect in three patients with acute myeloid leukemia.

*Methylglyoxal Bis (Guanylhydrazone) Diacetate.* Regelson and Holland (26) induced a brief reduction in w.b.c. in one case of acute monocytic leukemia with this chemical, but there was no clinical benefit, and the side effects of profound hypoglycemia and ulceration of the mouth and stomach were bad.

*Alkaloids.* Hodes *et al.* (15, 16) induced remissions with the alkaloid, vincaleukoblastine, extracted from *Vinca rosea Linn:* they described reductions in leukocyte count of all 12 patients with acute monocytic leukemia, while five experienced partial remissions; one of two children with acute lymphocytic leukemia also had a partial remission, and two with acute myelocytic leukemia were markedly improved. Warwick *et al.* (32) employed the same alkaloid to secure two partial responses for four and six weeks in five patients with acute leukemia.

## Discussion

Clinical trials, not previously reviewed, on a score of miscellaneous chemotherapeutic agents for the management of acute leukemia offer little promise of any of these proving superior to those which are already in wide use today. A number of these drugs failed to live up to their promise in screening tests with experimentally induced neoplasms in animals. This hard fact makes surveys of clinical trials with new miscellaneous chemicals all the more fruitful.

## Acknowledgments

The original literature for this study has been made available by the National Library of Medicine and the libraries of Furman University and Greenville General Hospital.

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# BOOK NOTICES

**Radioactive Substances,** by Marie Curie. Introduction by Alfred Del Vecchio. 94 pp. Philosophical Library, New York, 1961.

This book, published by the Philosophical Library, is a translation from the French of Marie Curie's thesis on radium, presented to the Faculty of Sciences in Paris. It traces the attempt of the famed husband and wife team to isolate and prepare, by new chemical means, the radio-active substance. The thesis is complete with the charts and graphs included by Mme. Curie in her thesis. This is another important book intended for English readers in the history of science. The text in spots is badly printed, but the importance of this classic must outweigh all such consideration.

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**Human Heredity,** by Jean Rostand. Translated from French by Wade Baskin. 139 pp. Philosophical Library, New York, 1961.

Dr. Jean Rostand is already widely known in this country from three of his works which have been translated into English; namely, *Adventures Before Birth* (Ryerson, 1936), *Life, the Great Adventure* (Scribner's, 1956), and *Can Man Be Modified?* (Basic Books, 1959). Now another of his popular science books has been translated in order to fill the demand of the reader unfamiliar with French. Dr. Rostand has long been aware of the need to educate and instruct the layman in the fields of modern scientific knowledge. *Human Heredity* is an attempt to present the layman with a clear and concise picture of the advances in the field of genetics. A clear English translation with an English bibliography, as well as a section of notes and an index, have been provided by Wade Baskin.

**Orientation in Pharmacy**—2nd edition, by Ralph W. Clark. 182 pp. Lea and Febiger, Philadelphia, 1961. Price $4.50.

This second edition of a book designed for pre-pharmacy students contains brief, interesting discussions of the history, ethics, economics, and requirements of pharmacy. A new chapter on the pharmacy library is included, as well as a useful supplementary reading list.

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**Microbial Cell Walls.** (Ciba Lectures in Microbial Biochemistry), by M. R. Salton. vii + 94 pp. John Wiley and Sons, Inc., New York, 1960. Price: $3.50.

This book, the fourth in the Ciba series of lectures in microbial biochemistry, is based on the lectures delivered at Rutgers University by M. R. Salton of the Department of Bacteriology, University of Manchester, England. It is an attempt to survey and summarize the many advantages in recent years in the study of the microbial cell wall. The three chapters deal with the application of the techniques of biophysics, chemistry, and biochemistry to one facet of microbial anatomy. Charts, diagrams, photographs, and an index accompany the text.

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**The Pfizer Handbook of Microbial Metabolites,** by Max W. Miller. 722 pp. incl. index. McGraw-Hill Book Co., New York, N. Y., 1961. Price: $15.00.

*The Pfizer Handbook of Microbial Metabolites,* the only reference work of its kind for biochemists and scientific workers in related fields, is the first effort to provide data on the source and the physical and chemical properties of all known metabolic products isolated from bacteria, molds, fungi, and lichens. It describes biosynthetic pathways to fermentation chemicals and contains information on large molecules whose importance in immunology and genetics is now widely recognized.

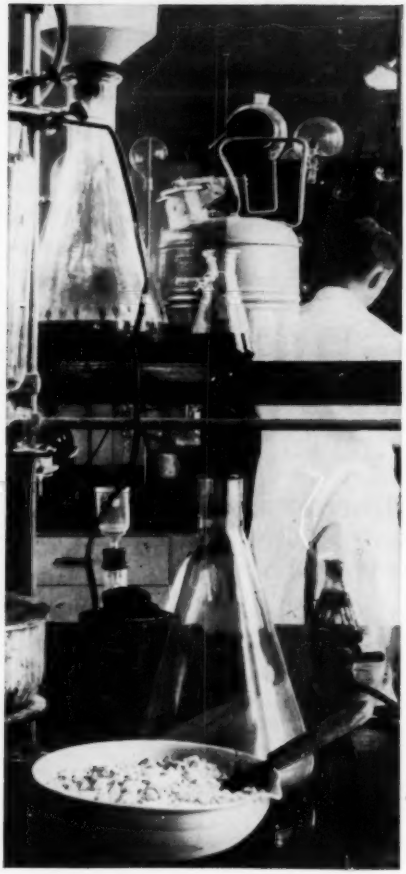
The Pfizer Handbook lists over 1300 metabolites with their physical and chemical properties, molecular structures, and the or-

ganisms involved in their production. The book covers a large number of *Streptomyces* metabolites, the genus of microorganisms which has been one of the richest sources of new antibiotics during the last ten years.

Information heretofore scattered through a wide variety of journals is presented in readily usable form for the first time. The volume, the results of several years of research and labor, was prepared on a non-profit basis as a service to science and education in the laboratories of Chas. Pfizer & Company, Inc., a pioneer in fermentation research since before World War I. It was compiled by Dr. Max W. Miller, a research chemist specializing in fermentation chemistry and the isolation of microbial products.

According to the Company, the book is an outgrowth of a mimeographed compilation used for several years as a reference source within the Pfizer research laboratories. The fact that no manual of this kind was heretofore available prompted publication of the handbook in greatly expanded form. The Pfizer Handbook lists approximately 1000 species of microorganisms. The book's Appendix "A" lists over 200 titles and references to publications dealing with the structure of large molecules produced by microorganisms, and a bibliography and general reference lists nearly 100 titles of related literature. Still another appendix on mycobacteria contains 200 references. Three separate indexes allow the reader to locate a compound by chemical name, by empirical formula, or by producing microorganism.

This handbook will help fill the need for a reference manual useful to scientists in fermentation research, and its use by teachers and students will contribute to the expansion of knowledge in biochemistry and related sciences.



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